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| <p>(21) International Application Number: PCT/US94/06607</p> <p>(22) International Filing Date: 22 June 1994 (22.06.94)</p> <p>(30) Priority Data:</p> <table border="0"><tr><td>08/081,567</td><td>23 June 1993 (23.06.93)</td><td>US</td></tr><tr><td>08/227,365</td><td>13 April 1994 (13.04.94)</td><td>US</td></tr></table> <p>(71)(72) Applicant and Inventor: MASIZ, John, J. [US/US]; 26 High Street, Topsfield, MA 01983 (US).</p> <p>(74) Agents: LEMACK, Kevin, S. et al.; Nields & Lemack, Suite 8, 176 E. Main Street, Westboro, MA 01581 (US).</p> | | 08/081,567 | 23 June 1993 (23.06.93) | US | 08/227,365 | 13 April 1994 (13.04.94) | US | <p>(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FL, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> |
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| 08/227,365 | 13 April 1994 (13.04.94) | US | | | | | | |
| <p>(54) Title: MOLECULAR TRANSDERMAL TRANSPORT SYSTEM</p> <p>(57) Abstract</p> <p>An efficient transdermal delivery system for delivering an active ingredient to the blood supply of a living body, comprising a vasodilator and/or topical counter irritant, an active ingredient, a permeation enhancer for the active ingredient, and a water soluble gum for binding the foregoing. A non-breathable layer also can be used for controlling the microenvironment at the transport site. Compression can be used to further enhance the blood supply at the transport site.</p> | | | | | | | | |

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MOLECULAR TRANSDERMAL TRANSPORT SYSTEMBACKGROUND OF THE INVENTION

Transdermal drug delivery offers many advantages over other
10 types of drug delivery. With transdermal delivery, a localized
delivery of drug molecules can be achieved, which makes
transdermal drug delivery target specific. Further, transdermal
drug delivery avoids the gastro intestinal complications caused
by oral delivery. While transdermal drug delivery offers these
15 and other advantages, a system than can quickly and reliably
deliver predictable quantities of drug molecules through the skin
has heretofore not been developed.

The evolution of transdermal drug delivery has centered
around patch technology. Patch technology is based on the
20 ability to hold an active ingredient in constant contact with the
epidermis. Over substantial periods of time, drug molecules,
held in such a state, will eventually find their way into the
bloodstream. Thus, patch technology relies on the ability of the
human body to pick up drug molecules through the skin.
25 Transdermal drug delivery using patch technology has recently
been applied for delivery of nicotine, in an effort to assist
smokers in quitting, the delivery of nitroglycerine to angina
sufferers, the delivery of replacement hormones in post
menopausal women, etc. These conventional drug delivery systems
30 comprise a patch with an active ingredient such as a drug
incorporated therein, the patch also including an adhesive for
attachment to the skin so as to place the active ingredient in

close proximity to the skin.

Problems with patch technology abound. First, active drug molecules have a difficult time passing through the skin, as the skin poses a significant barrier. In fact, in order for a drug molecule to reach the bloodstream, it must pass through the epidermis, stratum corneum (an especially dense layer of cells), dermis and capillary cell structure. Second, real world conditions such as the patient's obesity, metabolism and circulatory efficiency can effectively prevent transdermal drug delivery from occurring. Third, patch technology can be used only for treatments involving extensively long treatment periods, since the flow rate of drug molecules is so small. Finally, patch adhesion to the skin causes extensive skin trauma as well as cosmetic problems. Specifically, most adhesives currently used tend to aggressively adhere to the skin so that their removal may cause irritation and trauma. Indeed, subsequent patches used by a given individual are often applied to a different area of the skin in order to minimize such irritation and trauma.

In an effort to enhance the efficiency of transdermal drug delivery, the prior art teaches that by mixing certain individual ingredients (penetration enhancers) with a drug molecule, the ability of the drug molecule to pass through the skin is increased somewhat. For example, U.S. Patent No. 4,933,184 discloses the use of menthol as a penetration enhancer; U.S. Patent No. 5,229,130 discloses the use of vegetable oil (soybean and/or coconut oil) as a penetration enhancer; and U.S. Patent No. 4,440,777 discloses the use of eucalyptol as a penetration

enhancer.

Although mixing a penetration enhancer with a drug molecule helped to somewhat increase the speed of drug delivery, problems were still present. First, the aforementioned penetration enhancers constitute a passive, not an active, system. Thus, since they were not linked to the drug molecule, the penetration of the enhancer does not necessarily mean that the drug molecule has penetrated. In fact, the prior art drug molecule penetration is only a by-product of the enhancer penetration. Second, even when drug molecule penetration has occurred, the prior art does not establish a condition whereby the blood supply to the transport area is enhanced so as to maximize absorption speed. Third, prior art does not create a molecular structure that releases the drug molecule readily within the acidic medium that constitutes blood, so as to maximize bioavailability of the drug. Finally, although the prior art has increased the speed of transport of the drug molecule transdermally, it is still not sufficiently fast so as to eliminate (if desired) the need for a patch.

It is therefore an object of the present invention to provide a transdermal transport system that efficiently and easily allows for effective delivery of an active ingredient through the skin and into the blood supply of an animal or human.

SUMMARY OF THE INVENTION

The problems of the prior art have been overcome by the present invention, which provides an efficient, predictable and reliable active ingredient transdermal delivery system that is

sufficiently fast so as to eliminate (if desired) the need for a patch. More specifically, the present invention creates a molecular transdermal delivery vehicle that contains, as an integral part of the transdermal delivery molecule, the active
5 * drug molecule. This molecularly uninhibited lacteal ensemble (or "MULE") is constructed of four elements, namely, a vasodilator, a penetration enhancer, the active ingredient, and a water soluble gum for linking the vasodilator, penetration enhancer and active ingredient.

10 The advantages of the present invention over the prior art are many. First, the creation of a singular molecular unit that contains the drug molecule and transdermally transports it constitutes the first active system. Unlike the prior art, any degree of molecular penetration directly correlates to drug
15 molecule penetration, hence it is also predictable. Second, the MULE enhances blood flow to the transport/application site. Regardless of metabolism, obesity or circulatory efficiency, the vasodilatory aspect of the MULE maximizes blood flow to the transport site so as to reliably maximize absorption of the drug
20 molecule. Third, the MULE is constructed in a manner that when exposed to an acidic medium such as blood, it breaks apart, thereby releasing the drug molecule. This event insures bioavailability so that drug molecules are exposed to the blood supply and are capable of being picked up. Finally, the present
25 invention operates on transport speed that eliminates (if desired) the need for a patch.

DETAILED DESCRIPTION OF THE INVENTION

The invention comprises the creation of an molecular transdermal transport vehicle that has at least four components, including the active ingredient.

5 The first element of the MULE is one that enhances blood flow, through vasodilatory action, and/or through counter irritational action at the transport site. For example, topical counter irritants can be used, which are substances that provide a mild dermal irritation, generally creating a hot or cold
10 sensation in the area of application. This sensation results from the fact that the mild skin irritation brings blood closer to the surface of the skin, and can be utilized to enhance blood supply and effective transport of the active ingredient/carrier. Preferably, the nature and concentration of the counter irritant
15 in the MULE are those established by the Food and Drug Administration in the topical analgesic/topical counter irritant monographs for over-the-counter drugs, which monographs are herein incorporated by reference. For example, the counter irritants should be used in an amount effective for causing an
20 irritation, such as about 1% in the case where natural menthol is used as an external analgesic, and about 1-10% where natural menthol is used as a topical counter irritant. Suitable vasodilators or counter irritants include menthol, methyl salicylate, oil of wintergreen, peppermint oil, and capsicum,
25 with menthol being preferred.

The second element of the MULE is an ingredient that functions as a permeation or penetration enhancer. Suitable enhancers include vegetable oil or a vegetable oil/alcohol mix.

Suitable vegetable oils include peanut oil, olive oil, sunflower oil, soybean oil, monoi oil and macadamia oil, with olive oil being preferred. Suitable alcohols for the vegetable oil/alcohol mix include ethyl alcohol, isopropyl alcohol, methanol and witch
5 hazel. Olive oil mixed with isopropyl alcohol is a preferred vegetable oil/alcohol mix. Eucalyptol is a further suitable example of a vegetable oil/alcohol mix. Suitable ratios of vegetable oil:alcohol range from about 5:1 to about 1:10, preferably 1:2. Suitable amounts of vegetable oil or vegetable
10 oil/alcohol mix in the MULE range from about 1% to about 66% by weight, more preferably from about 10% to about 33.3% by weight.

The third element of the MULE is the active ingredient. The term "active ingredient" is used herein to indicate any material or composition desired to be delivered transdermally, especially
15 drugs. Examples of active ingredients that can be used in accordance with the present invention include acebutolol, acetaminophen, acetohydroxamic acid, acetophenazine, acyclovir, adrenocorticoids, allopurinol, alprazolam, aluminum hydroxide, amantadine, ambenonium, amiloride, aminobenzoate potassium,
20 amobarbital, amoxicillin, amphetamine, ampicillin, androgens, anesthetics, anticoagulants, anticonvulsants-dione type, antithyroid medicine, appetite suppressants, aspirin, atenolol, atropine, azatadine, bacampicillin, baclofen, beclomethasone, belladonna, bendroflumethiazide, benzoyl peroxide, benzthiazide,
25 benztropine, betamethasone, betha nechol, biperiden, bisacodyl, bromocriptine, bromodiphenhydramine, brompheniramine, buclizine, bumetanide, busulfan, butabarbital, butaperazine, caffeine, calcium carbonate, captopril, carbamazepine, carbenicillin,

carbidopa & levodopa, carbinoxamine inhibitors, carbonic
anhydrase, carisoprodol, carphenazine, cascara, cefaclor,
cefadroxil, cephalixin, cephradine, chlophedianol, chloral
hydrate, chlorambucil, chloramphenicol, chlordiazepoxide,
5 chloroquine, chlorothiazide, chlorotrianisene, chlorpheniramine,
chlorpromazine, chlorpropamide, chlorprothixene, chlorthalidone,
chlorzoxazone, cholestyramine, cimetidine, cinoxacin, clemastine,
clidinium, clindamycin, clofibrate, clomiphene, clonidine,
clorazepate, cloxacillin, colochicine, coloestipol, conjugated
10 estrogen, contraceptives, cortisone, cromolyn, cyclacillin,
cyclandelate, cyclizine, cyclobenzaprine, cyclophosphamide,
cyclothiazide, cycrimine, cyproheptadine, danazol, danthron,
dantrolene, dapsone, dextroamphetamine, dexamethasone,
dexchlorpheniramine, dextromethorphan, diazepam, dicloxacillin,
15 dicyclomine, diethylstilbestrol, diflunisal, digitalis,
diltiazem, dimenhydrinate, dimethindene, diphenhydramine,
diphenidol, diphenoxylate & atropine, diphenylpyraline,
dipyridamole, disopyramide, disulfiram, divalproex, docusate
calcium, docusate potassium, docusate sodium, doxylamine,
20 dronabinol, ephedrine, epinephrine, ergoloidmesylates, ergonovine,
ergotamine, erythromycins, esterified estrogens, estradiol,
estrogen, estrone, estropipate, ethacrynic acid, ethchlorvynol,
ethinyl estradiol, ethopropazine, ethosuximide, ethotoin,
fenopropfen, ferrous fumarate, ferrous gluconate, ferrous sulfate,
25 flavoxate, flecainide, fluphenazine, fluprednisolone, flurazepam,
folic acid, furosemide, gemfibrozil, glipizide, glyburide,
glycopyrrolate, gold compounds, griseofulvin, guaifenesin,
guanabenz, guanadrel, guanethidine, halazepam, haloperidol,

hetacillin, hexobarbital, hydralazine, hydrochlorothiazide,
hydrocortisone (cortisol), hydroflunethiazide,
hydroxychloroquine, hydroxyzine, hyoscyamine, ibuprofen,
indapamide, indomethacin, insulin, iofloquinol, iron-
5 polysaccharide, isoetharine, isoniazid, isopropamide
isoproterenol, isotretinoin, isoxsuprine, kaolin & pectin,
ketoconazole, lactulose, levodopa, lincomycin liothyronine,
liotrix, lithium, loperamide, lorazepam, magnesium hydroxide,
magnesium sulfate, magnesium trisilicate, maprotiline, meclizine,
10 meclofenamate, medroxyprogesterone, melenamic acid, melphalan,
mephenytoin, mephobarbital, meprobamate, mercaptopurine,
mesoridazine, metaproterenol, metaxalone, methamphetamine,
methaqualone, metharbital, methenamine, methicillin,
methocarbamol, methotrexate, methsuximide, methyclothazine,
15 methylcellulos, methyldopa, methylergonovine, methylphenidate,
methylprednisolone, methysergide, metoclopramide, metolazone,
metoprolol, metronidazole, minoxidil, mitotane, monamine oxidase
inhibitors, nadolol, nafcillin, nalidixic acid, naproxen,
narcotic analgesics, neomycin, neostigmine, niacin, nicotine,
20 nifedipine, nitrates, nitrofurantoin, nomifensine, norethindrone,
norethindrone acetate, norgestrel, nylidrin, nystatin,
orphenadrine, oxacillin, oxazepam, oxprenolol, oxymetazoline,
oxyphenbutazone, pancrelipase, pantothenic acid, papaverine,
para-aminosalicylic acid, paramethasone, paregoric, pemoline,
25 penicillamine, penicillin, penicillin-v, pentobarbital,
perphenazine, phenacetin, phenazopyridine, pheniramine,
phenobarbital, phenolphthalein, phenprocoumon, phensuximide,
phenylbutazone, phenylephrine, phenylpropanolamine, phenyl

toloxamine, phenytoin, pilocarpine, pindolol, piper acetazine,
piroxicum, poloxamer, polycarbophil calcium, polythiazide,
potassium supplements, pruzepam, prazosin, prednisolone,
prednisone, primidone, probenecid, probucol, procainamide,
5 procarbazine, prochlorperazine, procyclidine, promazine,
promethazine, propantheline, propranolol, pseudoephedrine,
psoralens, psyllium, pyridostigmine, pyrodoxine, pyrilamine,
pyrvinium, quineestrol, quinethazone, quinidine, quinine,
ranitidine, rauwolfia alkaloids, riboflavin, rifampin, ritodrine,
10 salicylates, scopolamine, secobarbital, senna, sannosides a & b,
simethicone, sodium bicarbonate, sodium phosphate, sodium
fluoride, spironolactone, sucruifate, sulfacytine,
sulfamethoxazole, sulfasalazine, sulfinpyrazone, sulfisoxazole,
sulindac, talbutal, tamazepam, terbutaline, terfenadine,
15 terphinyhydrate, teracyclines, thiabendazole, thiamine,
thioridazine, thiothixene, thyrolobulin, thyroid, thyroxine,
ticarcillin, timolol, tocinide, tolazamide, tolbutamide,
tolmetin trozodone, tretinoin, triamcinolone, trianterene,
triazolam, trichlormethiazide, tricyclic antidepressants,
20 tridhexethyl, trifluoperazine, triflupromazine, trihexyphenidyl,
trimeprazine, trimethobenzamine, trimethoprim, tripclennamine,
triprolidine, valproic acid, verapamil, vitamin A, vitamin B-12,
vitamin C, vitamin D, vitamin E, vitamin K and xanthine.

The final element that is essential to the creation of the
25 MULE is the addition of a water soluble gum. The water soluble
gum binds the first three elements of the MULE together into the
singular transport vehicle. Suitable water-soluble gums include
agar, arabic, carob, CMC, carrageenans, ghatti, guar, karaya,

kadaya, locust bean, tragacanth and xanthan gums. The water soluble gum should be used in an amount ranging from about 1% to about 33.3% by weight, most preferably an amount equal to the amount of active ingredient used.

5 The MULE is created by placing the penetration enhancer, the vasodilatory and/or counter irritant, and the active ingredient in a mixing vessel, and agitating the combination over a sufficient period to achieve a uniform mix. The water soluble gum is then slowly added while continuing the agitation. After
10 completion of the gum addition, agitation continues until mix uniformity is achieved. Other inactive ingredients may be added if desired.

 Although the MULE transports drug molecules so efficiently that the need for a patch is obviated, a patch can still be used
15 where desired. Pre-packaged patches, pre-impregnated with the MULE can make presorbed doses controllable. However, if a patch is used in conjunction with the MULE of the present invention, preferably the patch is a non-breathable layer on which the active ingredient is placed. Suitable non-breathable layers
20 include sheets of plastic, polyethylene, polyvinyl chloride, wax paper, foil, latex, etc., and combinations thereof. Those skilled in the art will recognize that any non-breathable substance (defined as a substance that does not allow the exchange of gases through its membrane) that is not deleterious
25 to the particular active ingredient being used and that does not cause any irritation upon contact with skin can be used.

 The non-breathable layer functions to create and control a suitable microenvironment at the transport site. Too cold an

environment can result in little blood supply to the dermal barrier; pores and other natural openings in the dermal barrier constrict, thereby preventing efficient transport. Too hot an environment can enhance secretion and perspiration and vapor flow through the dermal barrier, creating negative transport activity. Too dry an environment can cause an element or elements of the MULE to evaporate quickly, losing its ability to transport. The enhanced evaporation also creates negative transport pressure. Too humid an environment can cause dilution of the active ingredient, diminishing the capacity of the active ingredient and also creating negative transport activity.

The non-breathable layer captures the body temperature and humidity, thereby maintaining temperature at the most efficient for transport, the pore size at or close to a maximum, and normal blood flow to the site. In addition, since body vapor is captured, a proper moisture level is maintained. Preferably the temperature and humidity at the transport site is about 85-100°F and 50-99%, respectively. The non-breathable layer also creates a positive osmotic pressure back through the dermal layer, acting in a manner analogous to the so-called "greenhouse effect". Vapor admitted through the skin passes through the MULE, collects along the non-breathable barrier and then passes back through the MULE and through the skin. Since the temperature is at about the body temperature, the pore size is maximized and blood flow is sufficient so that the active ingredient can be easily picked up by the blood through the dermal layer. If desired, the non-breathable layer can be secured to the skin by any suitable means, such as with a bandage having adhesive or fasteners. In

the preferred embodiment, no adhesive is used, instead compression is used as discussed in detail below.

In order to further enhance blood supply to the transport site, compression can be utilized. Specifically, the non-breathable layer can be applied to the skin tightly, such as with a tightly wrapped bandage. Preferably the compression at the transport site is greater than zero pounds per square inch but less than about 10 pounds per square inch. Too much compression can result in restricted blood supply. The positive pressure applied also aids in forcing the MULE through the dermal layer and into contact with the blood supply.

The non-breathable layer and wrapping material can be conveniently designed to accommodate specific transport sites. For example, the non-breathable layer and wrap can be shaped in the form of a glove to be worn on one hand of the individual, or can be shaped in the form of a band to be worn on the arm or leg of the individual.

EXAMPLE 1

Vegetable oil, natural menthol and the active ingredient are placed in a mixing vessel. The contents are then agitated therein to achieve a uniform blend. Xanthan gum is then added slowly with the mixing vessel contents being continually agitated. The agitation continues until a uniform blend is achieved. Other inactive ingredients may be added, and again the contents mixed until uniformity is achieved.

The contents are removed from the mixing vessel and are applied directly to the skin at the desired transport site by

gentle massaging for approximately 60 seconds or until the mixture disappears.

What is claimed is:

1. A transdermal delivery system for delivering an active ingredient through the skin of a living body, comprising:

- a. an active ingredient;
- 5 b. first means for enhancing the blood supply to the site of transport of said active ingredient through said skin;
- c. second means for enhancing the permeation of said active ingredient through said skin; and
- 10 d. third means for binding said active ingredient and said first and second means into a singular transport vehicle.

2. The transdermal delivery system of claim 1, wherein said first means for enhancing the blood supply comprises a topical
15 counter irritant.

3. The transdermal delivery system of claim 2, wherein said topical counter irritant is selected from the group consisting of menthol, methyl salicylate, oil of wintergreen, peppermint oil and capsicum.

20 4. The transdermal delivery system of claim 1, wherein said second means for enhancing the permeation comprises a vegetable oil.

5. The transdermal delivery system of claim 2, wherein said second means for enhancing the permeation comprises a vegetable
25 oil.

6. The transdermal delivery system of claim 4, wherein said second means is selected from the group consisting of peanut oil, olive oil, sunflower oil, soybean oil, monoi oil, macadamia oil

and a vegetable oil/alcohol mix.

7. The transdermal delivery system of claim 5, wherein said second means is selected from the group consisting of peanut oil, olive oil, sunflower oil, soybean oil, monoi oil, macadamia oil and a vegetable oil/alcohol mix.

8. The transdermal delivery system of claim 1, wherein said third means comprises a water-soluble gum.

9. The transdermal delivery system of claim 2, wherein said third means comprises a water-soluble gum.

10. The transdermal delivery system of claim 5, wherein said third means comprises a water-soluble gum.

11. The transdermal delivery system of claim 8, wherein said water-soluble gum is selected from the group consisting of agar, arabic, carob, CMC, carrageenans, ghatti, guar, karaya, kadaya, locust bean, tragacanth and xanthan gum.

12. The transdermal delivery system of claim 9, wherein said water-soluble gum is selected from the group consisting of agar, arabic, carob, CMC, carrageenans, ghatti, guar, karaya, kadaya, locust bean, tragacanth and xanthan gum.

13. The transdermal delivery system of claim 10, wherein said water-soluble gum is selected from the group consisting of agar, arabic, carob, CMC, carrageenans, ghatti, guar, karaya, kadaya, locust bean, tragacanth and xanthan gum.

14. The transdermal delivery system of claim 1, further comprising means for controlling the temperature and humidity at the site of transport of said active ingredient through said skin.

15. The transdermal delivery system of claim 14, wherein

said means for controlling the temperature and humidity comprises a non-breathable layer.

16. A method of delivering an active ingredient through the skin of a living body, comprising:

- 5 a. placing the active ingredient on the skin at a transport site;
- b. enhancing the blood supply to the site of transport of said active ingredient through said skin by causing a skin irritation at said site; and
- 10 c. enhancing the permeation of said active ingredient through said skin by binding said active ingredient to a carrier with a water-soluble gum.

17. The method of claim 16, further comprising controlling the temperature and humidity at said transport site.

- 15 18. The method of claim 17, wherein said temperature and humidity are controlled by covering said transport site with a non-breathable material.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/06607

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61F 13/00

US CL : 424/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449, 447, 448

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS menthol, methylsalicylate, transdermal, agar, carrageenan, tragacanth, xanthan

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|--------------|---|-----------------------|
| X -- Y | US, A, 4,933,184 (TSUK) 12 June 1990, see column 2, lines 35-44 and column 5, lines 35-45. | 1-3 ----- 4-18 |
| Y,P | US, A, 5,229,130 (SHARMA ET AL) 20 July 1993, see column 2, lines 31-36; column 3, lines 1-8; column 6, lines 33-55. | 1-7,14,15, 17,18 |
| Y | THE MERCK INDEX: (WINDHOLZ), 1983, 10TH edition; "AN ENCYCLOPEDIA OF CHEMICALS, DRUGS, AND BIOLOGICALS", see pages 260, 660 and 1444. | 1,8-13,16 |
| A | US, A, 4,910,020 (SAMOUR) 20 March 1990, see entire document. | 14,15,17, 18 |
| A | US, A, 4,788,061 (SHORE) 29 November 1988, see entire document. | 14,15,17, 18 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| * "A" | Special categories of cited documents: document defining the general state of the art which is not considered to be part of particular relevance | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| "P" | document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

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Date of mailing of the international search report

26 SEP 1994

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